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Case Report

Metastatic ovarian papillary serous carcinoma to the breast: Diagnosis and pitfalls

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Introduction

Breast metastases from ovarian carcinoma (OC) have scarcely been reported. Morphologic and radiographic similarities between primary breast cancers (BC), and high grade papillary serous (PS) OC make distinguishing between the two diagnoses challenging, yet carry important consequences for treatment and prognosis. Herein, we describe a patient with a metastatic OC presenting with a palpable breast mass and discuss the utility of immunohistochemistry for distinguishing between OC and BC.

Case

A 52-year-old woman with no familial cancer history and an unknown BRCA-status presented with a palpable right breast mass. Four years earlier, she had been diagnosed with and treated for advanced stage high grade PS OC with neoadjuvant carboplatin–paclitaxel followed by an optimal interval cytoreductive surgery and additional chemotherapy. Her serum cancer antigen-125 (CA-125) normalized after treatment, and she had no evidence of disease. At the time of her first recurrence, 16-months later, her serum CA125 was 453U/mL and a biopsy of a xyphoid mass revealed recurrent high grade PS OC. A chest, abdomen, pelvic computed tomography (CT) scan also showed enlarged cervical lymph nodes and multiple solid nodules within the pelvis. The patient was re-treated with carboplatin–paclitaxel with a complete response, but her disease recurred 6-months later with supraclavicular, mediastinal, axillary, and retroperitoneal lymphadenopathy, a pleural effusion, and peritoneal nodularity, identified by CT imaging. The patient then began treatment with, but progressed through several regimens, including pegylated liposomal doxorubicin, weekly paclitaxel, topotecan, and a clinical trial regimen (docetaxel and an anti-vascular endothelial growth factor molecule). During the course of treatment for recurrent ovarian cancer, a breast exam revealed a 5 cm fixed right breast mass at the 9-o'clock position and right axillary lymphadenopathy. A mammogram showed a $5 \times 1.8 \times 1.6$ cm heterogeneous density with calcifications (BIRADS Category 4). The patient had no prior mammograms for comparison. Four ultrasound-guided core biopsies from the breast were evaluated by hematoxylin and eosin (H&E). Microscopically, the normal parenchyma was completely replaced by solid tumor with multiple areas showing a papillary pattern. Tumor cells exhibited moderate pleomorphism, prominent nucleoli, high nuclear-cytoplasmic ratio, and numerous mitoses (Fig. 1a, b).

Here, the main differential diagnoses were primary invasive micropapillary carcinoma (IMPC) of the breast versus metastatic PS OC. Immunohistochemical analyses of tumor cells for Paired-box-gene-8 (PAX8), Wilms' tumor-1 (WT1), cytokeratin (CK)7, CK20, CA125, gross cystic disease protein fluid (GCDPF-15)/BRST2, mammaglobin, Estrogen Receptor (ER), and Progesterone Receptor (PR) were positive for PAX8, WT1, CK7 and CA125, and negative for CK20, ER/PR, BRST2 and mammaglobin (Fig. 1c, d), thereby establishing a diagnosis of metastatic PS OC. After appropriate counseling regarding her overall clinical picture, the patient opted for best supportive care and passed away 3 months later.

Discussion

Secondary tumors to the breast are rare, accounting for approximately 2% of all malignant mammary tumors. The majority of metastases are from the contralateral breast, and the most common extramammary sites include lymphomas, melanomas, and those from the gastrointestinal tract (Georgiannos et al., 2001). Breast metastasis from primary OC is uncommon. Common modes of OC dissemination are via intraperitoneal implantation and lymphatic and hematogenous

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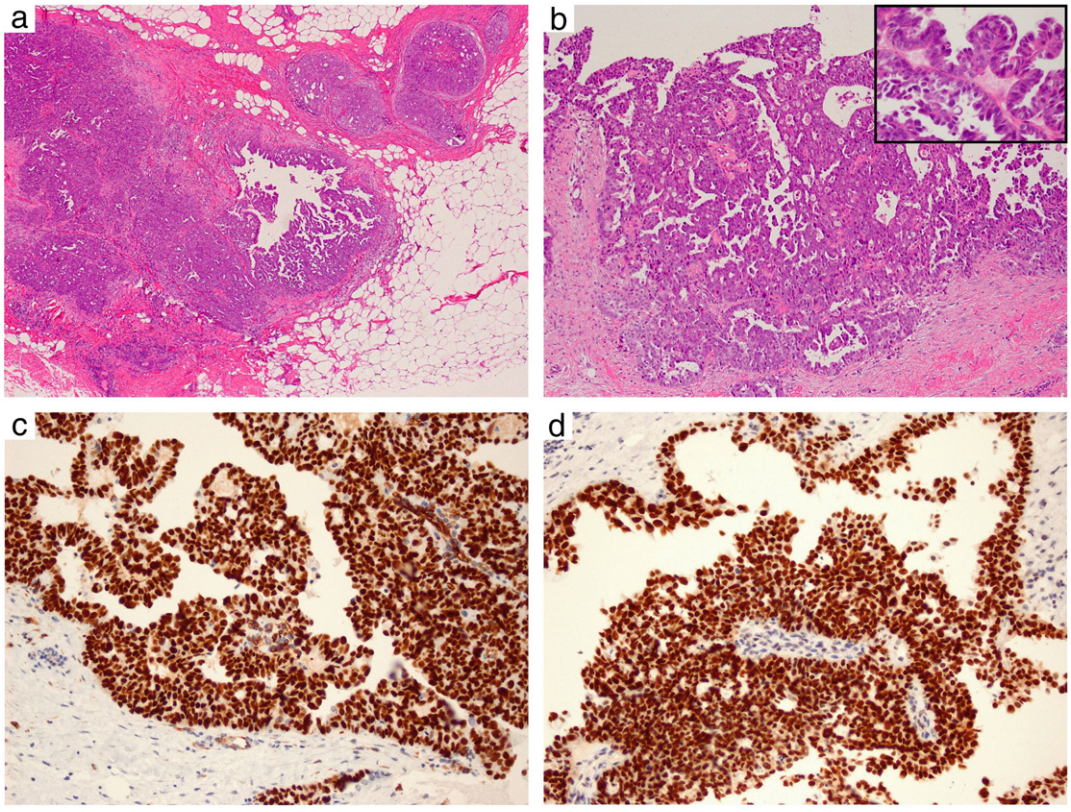

Fig. 1. a and b: The breast tissue was occupied by proliferation of neoplastic cells. The cells had a diffuse infiltrative pattern. However in areas the tumor exhibited a micropapillary pattern. (H&E ×20). (Insert) The tumor cells were moderately pleomorphic with high nuclear/cytoplasmic ratio and prominent nucleoli. Immunohistochemistry showed tumor cells to be diffusely and strongly positive for WT (c) and for PAX8 (d). Both expressions were in a nuclear pattern.

spread (Cormio et al., 2003). The liver and lung are the most common sites of distant OC metastasis, but factors favoring metastases to the breast include the absence of hereditary breast–ovarian cancer, a history of recurrent/advanced OC, and a shorter interval between OC diagnosis and development of breast mass (Georgiannos et al., 2001; Cormio et al., 2003).

Because the majority of metastatic OC are high grade PS, distinguishing them from breast IMPC is challenging. Mammographically, both lesions appear as heterogeneous masses with microcalcifications. Microscopically, both have marked nuclear atypia, brisk mitotic activity and papillary architectural patterns. The co-existence of ductal-carcinoma-in-situ (DCIS) favors primary BC; however, DCIS may be absent in biopsies due to sampling variability. Therefore, immunohistochemistry is an essential diagnostic adjunct.

OC and BC share many immunohistochemical profiles (e.g., ER, PR, HER2/*neu*, CA125, CK7, CK20) (Tornos and Solslow, 2005; Nonaka et al., 2008). Other candidate markers (e.g., GCDPF-15/BRST2, WT1, PAX8, PAX2, and mammaglobin) are also being considered (Ozcan et al., 2011; McKnight et al., 2010). GCDPF-15/BRST2 and mammaglobin have low sensitivity for BC, thereby limiting its diagnostic utility (Tornos and Solslow, 2005; Nonaka et al., 2008). WT1 and PAX8 appear to have the greatest utility in differentiating primary BC from metastatic OC due to their high sensitivity and low potential for aberrant expression. WT1 is detected in 94.7% of serous OC, 100% peritoneal serous carcinomas, and 2–3% IMPC, thereby limiting its utility here (Tornos and Solslow, 2005). PAX8, a transcription factor expressed in tumors of renal, mullerian and thyroid origin, is present in 99% of serous OC and absent in all BC including IMPC (Nonaka et al., 2008; Lotan et al., 2009). Thus, a positive PAX8 result here readily excludes primary BC. Although PAX2 is also a transcription factor essential in embryonic development of mullerian organs, PAX8 appears to be a superior epithelial marker for distinguishing metastatic mullerian epithelial tumors from normal and non-neoplastic tumors (Ozcan et al., 2011).

Distinguishing metastatic OC from primary BC has important prognostic and therapeutic implications. Because breast metastases commonly present in the setting of advanced-stage disease, overall survival is poor. Therapeutically, localized primary IMPC is managed mainly by surgical excision followed by chemoradiation, whereas metastatic OC to the breast here would represent recurrent OC and typically be treated with chemotherapy.

Summary

Although relatively uncommon, metastatic tumors to the breast should be appreciated so that a secondary malignancy from rare sites (e.g., ovary), is not overlooked. Accurate diagnosis of these metastases is important because the prognosis and therapies differ dramatically. While the clinical history and morphology can help distinguish between primary and metastatic BC, immunohistochemistry is essential when the diagnosis is still vague. PAX8 seems to be important in differentiating OC from BC. We recommend evaluating PAX8 immunohistochemistry when metastatic OC is suspected.

Conflict of interest statement

There is no conflict of interest.

References

Cormio, G., Rossi, C., Cazzolla, A., Resta, L., Loverro, G., Greco, P., Selvaggi, L., 2003. Distant metastases in ovarian carcinoma. Int. J. Gynecol. Cancer 13, 125–129.

Georgiannos, S.N., Aleong, J.C., Goode, A.W., et al., 2001. Secondary neoplasms of the breast. A survey of the 20th century. Cancer 92, 2259–2266.
Lotan, T.L., Ye, H., Melamed, J., Wu, X.R., IeM, Shih, JI, Epstein, 2009. Immunohistochemical panel to identify the primary site of invasive micropapillary carcinoma. Am. J. Surg. Pathol. 33, 1037–1041.
McKnight, R., Cohen, C., Siddiqui, M.T., 2010. Utility of paired box gene 8 (PAX8) expression in fluid and fine-needle aspiration cytology: an immunohistochemical study of metastatic ovarian serous carcinoma. Cancer Cytopathol. 25 (118), 298–302.
Nonaka, D., Chiriboga, L., Soslow, R.A., 2008. Expression of PAX8 as a useful marker in distinguishing ovarian carcinomas from mammary carcinomas. Am. J. Surg. Pathol. 32, 1566–1571.
Ozcan, A., Liles, N., Coffey, D., Shen, S.S., Truong, L.D., 2011. PAX2 and PAX8 expression in primary and metastatic Müllerian epithelial tumors: a comprehensive comparison. Am. J. Surg. Pathol. 35, 1837–1847.
Tornos, C., Solslow, R., Chen, S., et al., 2005. Expression of WT1, CA 125, and GCDFP-15 as useful markers in the differential diagnosis of primary ovarian carcinomas versus metastatic breast cancer to the ovary. Am. J. Surg. Pathol. 29, 1482–1489.